DETAILED ACTION

Status of Claims

1. Claims 1, 2, 4-6, and 8-10 are pending. Claims 1, 2, 4-6, and 8-10 are under consideration.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

2. Claims 1, 2, 4-6, and 8-10, as previously presented, are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A) A method of detecting mammalian embryonic stem cells undergoing differentiation comprising providing a culture of mammalian ES cells, embryonic carcinoma (EC) cell, or embryonic germ cells (EG) and detecting the cell surface expression of 5T4 antigen in said ES, EC, and EG cells, wherein 5T4 cell surface expression indicates that said ES cell, EC cell, or EG cells are undergoing differentiation.

B) An in vitro method of isolating mammalian embryonic stem cells undergoing differentiation comprising the method of A) and further comprising isolating said cells bound with said antibody, does not reasonably provide enablement for 1) a method of

determining differentiation status; and 2) a method of detecting, isolating, or sorting mammalian embryonic stem cells for stem cells undergoing differentiation wherein the absence of 5T4 antigen expression indicates undifferentiated stem cells.

The specification does not reasonably provide enablement for 1) a method of determining the differentiation status and 2) a method wherein the absence of 5T4 antigen expression indicates undifferentiated stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Applicant's arguments filed 7/18/2008 have been fully considered but they are not persuasive. Applicant asserts that Boyle et al provides no insight into the working of the present invention because Boyle et al does not provide any disclosure concerning the 5T4 expression status of mammalian embryonic stem cells that are differentiating. Applicant asserts that all the claimed methods concern detection or separation methods with a defined population of embryonic stem cells and therefore does not encompass detection of differentiated adult 5T4 antigen positive cells, as suggested in the enablement rejection (p. 4, last par, line 1 to p. 5, line 14 of remarks).

Applicant's arguments are not found persuasive. Applicant may intend to claim an invention that solely encompasses a population of cells consisting of stem cells wherein no linage restriction associated with adult stem cells are present. However, the breadth of the instant claims more broadly encompass heterogeneous population of stem cells that are at varying degrees of differentiation.

Applicant traversed this rejection on following grounds:

1) The instant claims are drawn to a method of detecting the differentiation status of a mammalian ES cell. The breadth of "detecting the differentiation status" encompasses a method that is capable of discerning undifferentiated embryonic stem cells, stem cells that have just entered the process of differentiation, intermediate precursor cells, last stage differentiating cells, and differentiated cells. However, the specification only teaches that 5T4 antigen is expressed immediately following the remove of LIF (p. 56, lines 25-30), therefore indicating that 5T4 antigen only corresponds with the early entry of an ES cell into the differentiation process. The specification fails to provide specific guidance to teach that 5T4 antigen would discern undifferentiated ES cells from intermediate precursor cells, or differentiated cells as is encompassed by the breadth of the claims. At the time of the invention, the art only teaches that 5T4 antigen expression is present in trophoblast cells and is upregulated in a variety of carcinoma cells (Boyle et al Hum Gen (1990) 84:455, col 1, par 1, of record in IDS). Therefore the art fails to teach 5T4 antigen as means of discerning the full breadth encompassed by differentiation status as well. Therefore, because the art and the specification fail to support the full breadth encompassed by "detecting the differentiation status", the specification does not enable the full breadth of "detecting the differentiation status" as claimed.

2) The claims encompass a method of detecting, isolating, or sorting mammalian ES cells, wherein the absence of 5T4 antigen expression indicates undifferentiated

stem cells (see claim 2) or cell not bound by 5T4 antigen antibody sort undifferentiated stem cells from stem cells undergoing differentiation.

To clarify this aspect of the enablement rejection, Applicant is referred to the art of Boyle et al. (1990). Boyle et al teaches that 5T4 antigen is expressed on the cell surface of trophoblast cells and amniotic epithelium. This is consistent with the teachings of the specification which disclosed that 5T4 antigen was originally isolated from human placental trophoblast cells (p. 3, lines 1-2). Boyle et al further teaches that the 5T4 antigen expression is limited to a few epithelial cells (p. 455, col 1, par 1). Since the art suggests that the 5T4 antigen is restricted to only a few differentiated cell types, the art is demonstrating that many adult differentiated epithelial cells and differentiated non-epithelial cells do not express 5T4 antigen. Therefore, the art implies that the absence of 5T4 antigen expression does not necessarily indicate that a stem cell is an undifferentiated stem cell because the absence of 5T4 antigen would not discern between an undifferentiated ES cell and a differentiated cell that does not express 5T4 antigen, as taught by Boyle et al. Therefore, because the art and the specification indicate that 5T4 antigen expression is not expressed in some differentiated cell types, a method that detects, isolates, or sorts out undifferentiated stem cells by the absence of 5T4 antigen expression or absence of binding to a 5T4 antigen antibody would not predictable identify or isolate undifferentiated stem cells as is encompassed by the claims. Therefore, the specification does not enable a method of detecting, isolating, or sorting out undifferentiated ES cells by the absence of 5T4 antigen or lack of binding to a 5T4 antigen antibody.

Applicant traverses this rejection as originally stated in the Non-Final Office action, mailed 7/27/2007. Applicant states the absence of differentiation markers, NF-68, and fgf-5, only indicates that the stem cell is not of that specific germ-layer lineage and does not necessarily indicate that the stem cell is not undergoing differentiation or is not a differentiated cell" (see page 6 of remarks, filed 11/27/2007). Applicant further points to Fig 12a and figures 24-27 to demonstrate that known undifferentiated ES cells expressing OCt-4 are not expressing 5T4 antigen in the presence of LIF but then begin to express 5T4 antigen when LIF is removed (pages 6 and 7 of remarks, filed 11/27/2007).

Applicant's arguments are not found persuasive. However, because the use of Ward et al in the enablement rejection of the Office Action, mailed 7/27/2007, may not have clearly demonstrated that the absence of 5T4 antigen does not necessarily indicate an undifferentiated ES cell, the rejection was reiterated above using the art of Boyle et al to clarify the rejection.

3) In the previous Office Action, mailed 7/27/2007, the breadth of the claims encompassed embryonic and adult stem cell. However, adult stem cells were deemed to lack enablement. (see par bridging pp. 6 and 7 and last par on p. 7). Applicant asserts that the claims have been amended to recite mammalian embryonic stem cell because Examiner indicated this as enabled subject matter. Applicant's argument is found persuasive. The amendment to the claims obviates this aspect of the enablement rejection. Therefore, this aspect of the enablement rejection is withdrawn.

4) The instant invention was deemed to lack enablement for detection and isolation of cells by using any means to detect 5T4 antigen. Applicant traverses this argument on the ground that the specification teaches multiple means of detecting 5T4 antigen including mRNA analysis (page 7 or remarks, filed 11/27/2007). This argument is not found persuasive because as previously indicated in the Office Action, mailed 7/27/2007, Ward et al teaches that 5T4 antigen was expressed in some embryonic stem cell populations that were and were not undergoing differentiation and that the expression of 5T4 antigen on the cell surface need to be the critical indicator rather than transcripts (par bridging pages 10 and 11).

Applicant also asserts that the claims have been amended to recite "detecting cell surface expression of 5T4 antigen". This argument is not found persuasive because claim 8 does not specify that the binding occurs with cell surface 5T4 antigen. Similarly claim 9 and 10 recite 5T4 antigen expression without specifying cell surface expression. Therefore, this ground of enablement is still present for these claims.

5) The instant invention was deemed to lack enablement for "differentiated stem cells". Applicant traverses this rejection on the grounds that the claims now encompass "undergoing differentiation" and this obviates the ground of enablement. Applicant's argument is found persuasive, and therefore, this issue of enablement is addressed by the amendments to the claims.

Because Applicant's amendment to the claims and arguments were unable to address and obviate all the issues of enablement of record, the instant scope of enablement rejection is maintained.

Therefore, in summary, the amendment to the claims and Applicant's arguments were not able to obviate all aspects of the enablement rejection of record. The specification and art still fail to support the full breadth of a method of detecting the differentiation status of a mammalian ES cell as claimed using 5T4 antigen, because 5T4 antigen only identifies cells in the early stages of differentiation. The specification also does not support a method that uses the absence of 5T4 antigen as an indicator of undifferentiated ES cell because the art teaches that the absence of 5T4 antigen would not discern between an undifferentiated cell and the many differentiated cells types that do not express 5T4 antigen as taught by Boyle et al. Therefore, the absence of 5T4 antigen expression or the lack of binding to a 5T4 antigen would not predictably identify, isolate, or sort out an undifferentiated ES cell as claimed. Because the above issues of enablement remain, the enablement rejection as previously and presently set forth is maintained.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites, "wherein said [embryonic] stem cells are embryonic germ cells or embryonal carcinoma cells". The instant recitation is indefinite because the claims

implies that embryonic germ cells and embryonal carcinoma cells are species of embryonic stem cells. In fact, an artisan would recognize that embryonic stem cells, embryonic germ cells, and embryonic carcinoma cells are distinct pluripotent cells types. The specification does not provide a definition that discloses a species of embryonic stem cell that is defined as an embryonic germ cell or embryonal carcinoma cell. Therefore, it is unclear how an embryonic germ or carcinoma cell is a species of embryonic stem cell, as implied by claim 4.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term is indefinite because the specification does not clearly redefine the term.

Amending claim 1 to recite "mammalian pluripotent stem cells" and amending claim 4 to recite, "wherein said stem cells are selected from the group consisting of embryonic stem cells, embryonic germ cells, and embryonic carcinoma cells" would be remedial.

Claim 8 recites, "A method of detecting differentiation status of a population of mammal embryonic stem cells". Applicant's use of this phrase in confusing in the light of the art recognized definition of embryonic stem cells. An embryonic stem cell by definite has the differentiated status of being undifferentiated. However, this phrase

implies that a population of embryonic stem cells can be in a "status" of being differentiated. This is inconsistent with art accepted understanding of embryonic stem cells. Amending the claims to recite, "A method of detecting differentiation status of a population of mammal embryonic cells" would be remedial.

Claim 9 recites, "undifferentiated mammalian embryonic stem cells". Applicant's use of the term is confusing because by definition mammalian embryonic stem cells are undifferentiated. Therefore, the claim implies the presences of differentiated embryonic stem cells, which is also confusing because an artisan would understand that once an embryonic stem cell has differentiated it no longer a stem cell. Therefore, the term is indefinite because the intended means of an undifferentiated mammalian embryonic stem cell in the context of the preamble and art recognized definition of the term, embryonic stem cell, renders the claims confusion. Claim 10 depends from claim 9.

Amending claim 9 to recite, "separating embryonic stem cells from embryonic cells undergoing differentiation from a mixture of mammalian embryonic stem cells and mammalian embryonic cells undergoing differentiation" would be remedial.

4. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Marcia S. Noble